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L7: Entry 85 of 255 File: USPT Jan 28, 2003

DOCUMENT-IDENTIFIER: US 6511749 B1
TITLE: Preparation of multiwall polymeric microcapsules from hydrophilic polymers

Brief Summary Text (15):
In the preferred embodiment, two hydrophilic polymers are dissolved in an aqueous solution, a substance to be incorporated is dispersed or dissolved in the polymer solution, the mixture is suspended in a continuous phase, and the solvent is slowly evaporated, creating microspheres with an inner core formed by one polymer and an outer layer of the second polymer. The continuous phase can be either an organic oil, a volatile organic solvent, or an aqueous solution containing a third polymer that is not soluble with the first mixture of polymers and which will cause phase separation of the first two polymers as the mixture is stirred.

Detailed Description Text (40):
Multi-layer polymeric microcapsule delivery systems may be prepared which include a substance, such as a bioactive agent in the polymeric layers. In one embodiment, first and second polymers are dissolved in an aqueous solution, the substance to be encapsulated is dispersed or dissolved in the polymer solution, and the mixture is suspended in a third solution which can be either an organic solvent or an organic oil, or an aqueous solution containing a third polymer, wherein the first two polymers are not soluble in the third solution. The mixture is stirred to form an emulsion of the first two polymers in the third continuous phase, and the solvent is slowly evaporated, creating microspheres with an inner core of the first polymer and an outer layer of the second polymer. In another embodiment, the rate of evaporation may be accelerated if necessary to promote the formation of the outer layer of the second polymer and then the core of the first polymer.

Detailed Description Text (42):
In one embodiment, a solvent evaporation technique may be used to make polymeric microspheres. In this embodiment, two polymers are dissolved in an aqueous solvent in which each polymer is soluble, at concentrations slightly above or at the cloud point of the two polymer solution. The resulting solution or suspension of the two polymers in solvent is then added to an organic or aqueous solution containing a different polymer that forces the first two polymers to phase separate, wherein the different polymer will not be part of the final product and is used only as a phase inducer, creating solid microspheres as the solvent evaporates. As the polymers become more concentrated, they begin to phase separate and if given enough time will configure themselves in their most thermodynamically stable configuration as dictated by the spreading coefficient theory described above. When the rate of solvent removal is increased, kinetic factors determine the extent of spreading, often trapping the spheres in a non-equilibrium configuration.

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L7: Entry 137 of 255 File: USPT Feb 9, 1999

DOCUMENT-IDENTIFIER: US 5869103 A
TITLE: Polymer microparticles for drug delivery

Detailed Description Text (19):
The emulsification/solvent evaporation technique for preparation of PLG microparticles is generally based on the use of immiscible liquids to form droplets of polymer solution in a continuous phase which subsequently harden to form microparticles by polymer precipitation and solvent removal. An exception is the nanoprecipitation method of Fessi et al. in which spherical particles may be produced by adding a solution of PLG in acetone to water.

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L7: Entry 151 of 255 File: USPT Jan 6, 1998

DOCUMENT-IDENTIFIER: US 5705197 A
TITLE: Extraction process for producing PLGA microspheres

Brief Summary Text (5):
Control of the size range of microspheres produced by the hydrid process of the invention is achieved by selecting an emulsion oil in which the polymer solvent exhibits the appropriate solubility at the temperature and presssure of the evaporative phase. Greater solubility results in small spheres, while a lesser solubility results in larger diameter spheres.

Detailed Description Text (52):
The microspheres diameters produced by our hybrid evaporation-extraction process can be predictably influenced by control of the temperature during the evaporative phase of the process provided that the temperature is kept below 30.degree. C. The size ranges produced by this process are suitable for use in delivery of biologically active substances or vaccine antigens to the intestinal mucosa.

L7: Entry 160 of 255 File: USPT Mar 11, 1997

DOCUMENT-IDENTIFIER: US 5609886 A
TITLE: Microspheres for the controlled release of water-soluble substances and process for preparing them

Brief Summary Text (35):
e) the two solvents are then removed from the microspheres being formed, with stirring, the first solvent being removed by evaporation, the second solvent as well as part of the first solvent which is miscible therewith passing into the aqueous phase by a mechanism of phase separation,

Brief Summary Text (43):
Thus, contrary to the conventional method by emulsion/evaporation where the hardening of the microsphere is carried out solely by simple and slow evaporation of the polymer solvent such as CH.sub.2 Cl.sub.2, in the method according to the present invention, the phenomenon is linked simultaneously to the evaporation of the said first solvent such as CH.sub.2 Cl.sub.2 and to a rapid phase separation of the second solvent such as DMA towards the aqueous phase. Through the miscibility of the two solvents, some of the first solvent also accompanies the second towards the aqueous phase which considerably reinforces and accelerates its extraction. The method thus combines the processes of evaporation and phase separation by substantially modifying the kinetics of extraction of the solvents as compared with a traditional method of emulsion/evaporation. The kinetics of the incorporation process is therefore modified, which contributes, with the homogeneity of the distribution, to the high level of incorporation observed, as will be described later.

Detailed Description Text (35):
In the methods, the aqueous phase consists of 75 ml of 4% gelatin in water (weight/volume). The two phases are emulsified by stirring with a helix at 1,500 revolutions/minute for 1 minute. A stirring of 500 revolutions/minute is maintained, on the one hand, in order to facilitate the evaporation of the CH.sub.2 Cl.sub.2 and, on the other hand, in the method according to the invention, to enable the DMA to be extracted in the aqueous phase, in both cases, the microspheres are washed in water and collected on sieves.

CLAIMS:

2. Microspheres obtained by a process comprising steps of:

a) dissolving a biocompatible and biodegradable polymer in a first volatile organic solvent immiscible with water,

b) separately dissolving a water-soluble polypeptide in a second solvent which is nonvolatile, miscible with said first solvent, a solvent for said polymer, and miscible with water,

c) mixing the solution of said polypeptide and the solution of said polymer to produce an organic phase containing said polymer and said polypeptide,

d) emulsifying said organic phase in an immiscible dispersant aqueous phase containing an emulsifying agent,

e) removing the two solvents from the microspheres being formed, with stirring, the

first solvent being removed by evaporation, the second solvent as well as part of the first solvent which is miscible therewith being removed by passage towards the aqueous phase by a mechanism of phase separation, and

f) after removal of the solvents, recovering the microspheres formed, optionally after washing in water and sieving.

L7: Entry 161 of 255 File: USPT Feb 18, 1997

DOCUMENT-IDENTIFIER: US 5603960 A
TITLE: Preparation of microparticles and method of immunization

Brief Summary Text (7):
There are several methods known for the production of microparticles. Typical methods for producing microparticles include solvent evaporation and phase separation. With production methods such as solvent evaporation, as much as 50% w/w of insoluble or poorly soluble materials, may be incorporated in biodegradable microparticles. However, with more water soluble materials, such as peptides, drug loadings have generally been much lower.

Brief Summary Text (9):
A variety of techniques to produce microparticles have been described in the prior art. For example, United Kingdom Patent Application No. 2,234,896 to Bodmer et al. describes a method of forming microparticles by mixing a solution of the polymer dissolved in an appropriate solvent with a solution of a drug. Microparticle formation is then induced by the addition of a phase inducing agent. European Patent Application 0 330 180 to Hyon et al. describes a process for preparing polylactic acid-type microparticles by adding a solution of a drug and a polymer in a mixed solvent to a phase inducing agent and evaporating the original solvent microparticle formation. Other examples of processes for preparing microparticles by phase separation technique have been described in U.S. Pat. Nos. 4,732,763 to Beck et al. and 4,897,268 to Tice et al. and by Ruiz et al. in the International Journal of Pharmaceutics (1989) 49:69-77 and in Pharmaceutical Research (1990) 9:928-934.

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L7: Entry 164 of 255 File: USPT Sep 17, 1996

DOCUMENT-IDENTIFIER: US 5556642 A
** See image for Certificate of Correction **
TITLE: Method for producing sustained release microsphere preparation

Brief Summary Text (9):
However, the conventional method for producing microspheres from O/W emulsion, i.e. the method which comprises dispersing a medicament powder into an oil phase to give an O/W emulsion, followed by removing solvents by the solvent evaporation method, or dissolving a water-soluble medicament in an oil phase containing a water-miscible organic solvent to give an O/W emulsion, followed by removing solvents by the solvent evaporation method, have some defects. For example, there is burst-effect (rapid release of medicament within a short period of time), or suitable species of medicaments and biodegradable polymer are limited. In O/W method wherein the medicament crystals are dispersed into oil phase, the water-soluble medicament is not dissolved in the oil phase (i.e. the polymer phase), and hence, the medicament exists heterogeneously in the oil phase in the form of crystalline particles. As a result, the medicament leaks out into the external aqueous solution in the emulsification step, which causes extremely low incorporation efficiency of the medicament into the microspheres. Besides, crystals of the medicament make pores on the surface of the microspheres being solidifying during emulsification, which often leads to an initial burst as mentioned above.

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L7: Entry 187 of 255 File: USPT Jan 1, 1991

DOCUMENT-IDENTIFIER: US 4981696 A
TITLE: Polylactide compositions

Brief Summary Text (47):
In the evaporation process, drug-loaded microspheres are prepared by dissolving the polylactide and dissolving or suspending the active ingredient in a solvent such as methylene chloride. The drug/polymer/solvent is emulsified in a 5% aqueous solution of polyvinyl alcohol where the polyvinyl alcohol which acts as an emulisifier allows control of the droplet size of the drug/polymer/solvent by agitation. When the desired droplet size is achieved, the emulsion is stirred at a constant rate to allow the methylene chloride to evaporate from the system. Evaporation can occur at atmospheric or reduced pressure and at a variety of temperatures. Once a significant portion of the solvent is removed, agitation may be stopped, allowing the partially solidified microspheres to settle. Optionally, the polyvinyl alcohol, aqueous solution can be replaced with water, and any remaining solvent can be removed by continued evaporation. Upon completion of evaporation, the spheres can be isolated and dried. A number of variables affect the product quality of microspheres produced from the solvent evaporation process including the organic solvent, temperature of evaporation, volume of organic phase/aqueous phase, the nature and amount of emulsifier in the aqueous phase, polymer structure and molecular weight, and solubility of the drug being encapsulated.

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L7: Entry 232 of 255 File: DWPI Aug 27, 2002

DERWENT-ACC-NO: 2002-730561
DERWENT-WEEK: 200279

TITLE: Preparation of microparticles useful for drug delivery involves mixing two phases containing active agent and surfactant to form emulsion and extraction followed by evaporation

Basic Abstract Text (1):
NOVELTY - Preparation of microparticles involves mixing a first phase (p1) comprising a solution of an excipient dissolved in a first solvent (s1) and a second phase (p2) comprising a second solvent (s2) and a surfactant to form an emulsion (e) having microdroplets comprising (p1), then mixing a portion of an extraction phase (p3) in (e) to initiate hardening of the microdroplets forming microparticles followed by evaporation.

Basic Abstract Text (11):
ADVANTAGE - The microparticles effectively encapsulate active agent. The amount of extraction medium required is minimized in the process. The emulsion-based methods provide microparticles in an efficient batch or continuous process and the brief extraction step prior to evaporation minimizes the loss of active agent from the microparticles and reduces the required volume of extraction phase as compared to other extraction-based processes.

Standard Title Terms (1):
PREPARATION MICROPARTICLES USEFUL DRUG DELIVER MIX TWO PHASE CONTAIN ACTIVE AGENT SURFACTANT FORM EMULSION EXTRACT FOLLOW EVAPORATION

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L7: Entry 235 of 255 File: DWPI Jun 10, 1999

DERWENT-ACC-NO: 1999-418456
DERWENT-WEEK: 200046

TITLE: Production of porous microspheres

Basic Abstract Text (1):
NOVELTY - A new process for producing porous microspheres having a diameter of 3 - 300 microns comprises mixing an organic phase and an aqueous phase under emulsifying conditions and evaporating the solvent.

L7: Entry 244 of 255 File: DWPI Sep 5, 1991

DERWENT-ACC-NO: 1991-281266
DERWENT-WEEK: 200124

TITLE: Biodegradable microspheres for controlled release of polypeptide - have matrix of biocompatible polymer, are prepd. using both evaporation and phase sepn.

Equivalent Abstract Text (1):
Process for preparing microparticles of the microsphere type of a water-soluble and a biocompatible and biodegradable polymer controlling the kinetics of release of the said substance consisting of a matrix of the said polymer within which the said water-soluble substance is regularly dispersed, characterised in that a) the said polymer is dissolved in a first volatile organic solvent immiscible with water, b) the said water-soluble substance is separately dissolved in a second solvent which is miscible with the said first solvent, is a solvent for the polymer, and miscible with water, the proportion of second solvent to first solvent ranging from 5/95 to 70/30 by volume, c) the solution of the said substance and the solution of the said polymer are mixed, d) an organic phase of the polymer and of the said substance is obtained which is then emulsified in an immiscible dispersant medium consisting of an aqueous phase containing an emulsifying agent, e) the two solvents are then removed from the microspheres being formed with stirring, the first solvent being removed by evaporation, the second solvent as well as part of the first solvent which is miscible therewith being removed by passage towards the aqueous phase by a mechanism of phase separation, f) after removal of the solvents, the microspheres formed are recovered, optionally after washing in water and sieving.

Equivalent Abstract Text (2):
Process for preparing microparticles of the microsphere type of a water-soluble polypeptide or a pharmaceutically acceptable salt and a biocompatible and biodegradable polymer, comprising: a) dissolving a biocompatible and biodegradable polymer in a first volatile organic solvent immiscible with water; b) separately dissolving water-soluble polypeptide in a second solvent which is nonvolatile, miscible with said first solvent, a solvent for said polymer, and miscible with water; c) mixing the solution of said polypeptide and the solution of said polymer to produce an organic phase containing said polymer and said polypeptide; d) emulsifying said organic phase in an immiscible dispersant aqueous phase containing an emulsifying agent; e) removing the two solvents from the microspheres being formed, with stirring, the first solvent being removed by evaporation, the second solvent as well as part of the first solvent which is miscible therewith being removed by passage towards the aqueous phase by a mechanism of phase separation; and f) after removal of the solvents, recovering the microspheres formed, optionally after washing in water and sieving.

Standard Title Terms (1):
BIODEGRADABLE MICROSPHERE CONTROL RELEASE POLYPEPTIDE MATRIX BIOCOMPATIBLE POLYMER PREPARATION EVAPORATION PHASE SEPARATE

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L7: Entry 15 of 255 File: PGPB Jul 10, 2003

DOCUMENT-IDENTIFIER: US 20030129249 A1
TITLE: Preparation of biodegradable, biocompatible microparticles containing a biologically active agent

Summary of Invention Paragraph (12):
[0012] Tice et al, in U.S. Pat. No. 4,530,840, describe the preparation of microparticles containing an anti-inflammatory active agent by a method comprising: (a) dissolving or dispersing an anti-inflammatory agent in a solvent and dissolving a biocompatible and biodegradable wall forming material in that solvent; (b) dispersing the solvent containing the anti-inflammatory agent and wall forming material in a continuous-phase processing medium; (c) evaporating a portion of the solvent from the dispersion of step (b), thereby forming microparticles containing the anti-inflammatory agent in the suspension; and (d) extracting the remainder of the solvent from the microparticles.

L7: Entry 81 of 255 File: USPT Mar 4, 2003

DOCUMENT-IDENTIFIER: US 6528035 B1
TITLE: Multiwall polymeric microcapsules from hydrophilic polymers

Brief Summary Text (14):
In the preferred embodiment, two hydrophilic polymers are dissolved in an aqueous solution, a substance to be incorporated is dispersed or dissolved in the polymer solution, the mixture is suspended in a continuous phase, and the solvent is slowly evaporated, creating microspheres with an inner core formed by one polymer and an outer layer of the second polymer. The continuous phase can be either an organic oil, a volatile organic solvent, or an aqueous solution containing a third polymer that is not soluble with the first mixture of polymers and which will cause phase separation of the first two polymers as the mixture is stirred.

Detailed Description Text (38):
Multi-layer polymeric microcapsule delivery systems may be prepared which include a substance, such as a bioactive agent in the polymeric layers. In one embodiment, first and second polymers are dissolved in an aqueous solution, the substance to be encapsulated is dispersed or dissolved in the polymer solution, and the mixture is suspended in a third solution which can be either an organic solvent or an organic oil, or an aqueous solution containing a third polymer, wherein the first two polymers are not soluble in the third solution. The mixture is stirred to form an emulsion of the first two polymers in the third continuous phase, and the solvent is slowly evaporated, creating microspheres with an inner core of the first polymer and an outer layer of the second polymer. In another embodiment, the rate of evaporation may be accelerated if necessary to promote the formation of the outer layer of the second polymer and then the core of the first polymer.

Detailed Description Text (41):
In one embodiment, a solvent evaporation technique may be used to make polymeric microspheres. In this embodiment, two polymers are dissolved in an aqueous solvent in which each polymer is soluble, at concentrations slightly above or at the cloud point of the two polymer solution. The resulting solution or suspension of the two polymers in solvent is then added to an organic or aqueous solution containing a different polymer that forces the first two polymers to phase separate, wherein the different polymer will not be part of the final product and is used only as a phase inducer, creating solid microspheres as the solvent evaporates. As the polymers become more concentrated, they begin to phase separate and if given enough time will configure themselves in their most thermodynamically stable configuration as dictated by the spreading coefficient theory described above. When the rate of solvent removal is increased, kinetic factors determine the extent of spreading, often trapping the spheres in a non-equilibrium configuration.